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| 10/603,369 | 06/25/2003 | David Nathan Abraham Fox | 16789 (PC25204) | 2797 |

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| EXAMINER | |
|---|---|
| ROYDS, LESLIE A | |

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|---|---|
| 1614 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/603,369 | FOX ET AL. | |
| | Examiner | Art Unit | |
| | Leslie A. Royds | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *13 June 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

**Claims 1-13 are presented for examination.**

Applicant's Amendment filed June 9, 2005 has been received and entered into the application. Accordingly, the title, the specification at page 6 and claims 1-2, 4, 7 and 9 have been amended. Applicant's Information Disclosure Statement (IDS) filed June 13, 2005 has also been received and entered into the application. As reflected by the attached, completed copy of form PTO-1449 (five pages total), the Examiner has considered the cited references.

In view of the above amendments and Applicant's remarks, the objection to claims 4-8 for improper multiple dependency; the objection to claims 2 and 9 for minor informalities; the objection to the title; the objection to the specification for improper incorporation by reference; the rejection of claims 1-3 and 9 under 35 U.S.C. §101; the rejection of claims 1-3 and 9 under 35 U.S.C. §112, first paragraph; and the rejection of claims 1-3 and 9 under 35 U.S.C. §112, second paragraph; are each hereby **withdrawn**.

### *Objections to the Oath/Declaration*

The Examiner has noted Applicant's pending submission of a newly executed oath. The present objection to the oath/declaration will be maintained until the Office has received such a submission.

***(i) Priority Claim on Oath/Declaration***

Receipt is acknowledged of papers filed under 35 U.S.C. 119 (a)-(d) based on United Kingdom Application No. 0214784.1 filed on June 26, 2002. Applicant has not complied with the requirements of 37 CFR 1.63(c), since the oath/declaration does not acknowledge the filing

of any foreign application. Submission of a new oath/declaration with reference to the foreign application is required. See MPEP §202.01 and §202.04 and 37 C.F.R. 1.63 and 1.78.

***(ii) Missing Residence and Postal Addresses on Oath/Declaration***

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by serial number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because it does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either on an application data sheet or supplemental oath or declaration. Appropriate correction is required.

***Objection to the Title (New Ground of Objection)***

The Examiner has noted that the title of the application has been amended to "Pharmaceutical Combinations Comprising a PDE 5 Inhibitor and an Angiotensin II Receptor Antagonist for the Treatment of Hypertension" at page 12 of Applicant's remarks. However, the amendments to the specification at page 2 of Applicant's remarks show that the title has been amended to ---PHARMACEUTICAL COMPRISING A PDE 5 INHIBITOR AND AN ANGIOTENSIN II RECEPTOR ANTAGONIST FOR THE TREATMENT OF HYPERTENSION---. Applicant is requested to amend the title in the following manner to be consistent with the remarks made herein:

---Pharmaceutical Combinations Comprising a PDE 5 Inhibitor and an Angiotensin II Receptor Antagonist for the Treatment of Hypertension---.

***Objection to the Specification (New Ground of Objection)***

The amendment filed June 9, 2005 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material that is not supported by the original disclosure is as follows:

The incorporation by reference of United States Patent Nos. 6,743,719 (drawn to a method for forming a conductive copper structure); 5,728,862 (drawn to a method for preparing and purifying N-alkylated aspartame derivatives); 6,004,938 (drawn to inositolglycans having insulin-like action); 6,232,306 (drawn to derivatives of 3-(2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl)-cephams); 6,472,525 (drawn to hexaazaisowurtzitane derivatives and methods for producing the same); 6,573,279 (drawn to isoquinoline derivatives or salts thereof); and 6,576,761 (drawn to a process for the preparation of cephem compounds) in response to the objection to the improper incorporation by reference of foreign patents and foreign patent application and publications adds material to the specification that was not present or suggested in the specification as originally filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

***Claim Rejection - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7, 9-11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Macor et al. (U.S. Patent No. 6,087,368; 2000), already of record, for the reasons of record as set forth in the previous Office Action dated March 7, 2005 at pages 12-15, as applied to claims 1-3, 9-11 and 13.

Present claims 4-5 and 7 are properly included in the instant rejection because Applicant has amended the claims to correct improper multiple dependency. The teachings of Macor et al. directly anticipate the limitations of present claims 4-5 and 7. The reference teaches the use of sildenafil (col.19, line 6; see present claims 4-5) and the carbazoles taught in WO 95/19978 (col.19, lines 14-15; see examples 1, 3, 7-8, 78 and 95 of WO 95/19978, which correspond to Applicant's presently claimed tadalafil of instant claim 5) and losartan, irbesartan, valsartan or candesartan (col.19, lines 10-11; see present claim 7).

Applicant's remarks at pages 13-15 of the amendment have been carefully considered, but fail to persuade the Examiner of error in her determination of anticipation.

Applicant states that Macor et al. does not teach the use of a cGMP PDE5 inhibitor in combination with an angiotensin II antagonist for the treatment of hypertension and atherosclerosis and further states that Macor et al. discloses, in general terms and without any substantial evidence, that the compounds disclosed therein may be employed in combination with other suitable therapeutic agents useful in the treatment of cGMP-associated conditions. Applicant submits that Macor et al. fails to teach all of the limitations of claim 1 and, thus, does not anticipate claim 1 or the dependent claims thereof.

Applicant's assertion that Macor et al. fails to teach the use of a cGMP PDE5 inhibitor in combination with an angiotensin II antagonist for the treatment of hypertension and atherosclerosis is not a point well taken. Applicant's attention is drawn directly to the reference, specifically at the portions cited in the rejection made of record in the previous Office Action. Macor et al. expressly discloses compounds that inhibit cGMP PDE5, which are useful in the treatment of cGMP-associated conditions (col.16, lines 51-54) and specifically discloses the following cardiovascular disorders as being responsive to inhibition of cGMP PDE: hypertension, angina (stable, unstable and variant type), congestive heart failure, atherosclerosis and stroke (col.1, lines 55-61 and col.16, line 66-col.17, line 9). Macor et al. further teaches that the disclosed compounds may be employed alone or in combination with other suitable therapeutic agents useful in the treatment of cGMP-associated conditions, such as angiotensin II antagonists, particularly losartan, irbesartan, valsartan or candesartan (col.18, line 60-col.19, line 3 and col.19, lines 10-11).

While Applicant alleges that the disclosure of the cGMP PDE5 compounds of Macor et al. in combination with other suitable therapeutic agents useful in the treatment of cGMP-associated conditions is made in general terms and without any substantial evidence, such an allegation does not change the fact that the reference expressly and explicitly teaches the use of a cGMP PDE5 inhibitor in combination with an angiotensin II antagonist for the treatment of any disorder responding to the inhibition of cGMP PDE, such as the various cardiovascular disorders stated in the reference at col.1, lines 55-61 and col.16, line 66-col.17, line 9. In light of such a teaching, Applicant's premise that Macor et al. does not specifically disclose which cGMP-associated condition can be treated with the combined use of the disclosed compounds and other

suitable therapeutic agents is inherently flawed. Macor et al. teaches that the combination of the cGMP PDE5 inhibitor compound and an angiotensin II antagonist may be employed in the treatment of the genus of cGMP-associated conditions, of which hypertension, angina (stable, unstable and variant type), congestive heart failure, atherosclerosis and stroke are specifically taught, which is considered express, explicit disclosure.

Thus, Macor et al. teaches each and every limitation of the presently claimed invention to which the reference is applied. Applicant is further reminded that the recitation of limitations in the alternative will render the claim rejected as long as at least one of the limitations listed in the alternative is taught by the reference (see, for example, present claims 1 or 4). For this reason, those stated above and those set forth in the previous Office Action, claims 1-5, 7, 9-11 and 13 are properly rejected.

***Claim Rejection - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Grounds of Rejection

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Macor et al. (U.S. Patent No. 6,087,368; 2000), in view of The Merck Manual of Diagnosis and Therapy (Sixteenth Edition; 1992, p.413-431), Cecil's Textbook of Medicine (Twenty-First Edition, 2000, 273-279 and 1279-1285), and Physician's Desk Reference (55th Edition, 2001; p.323 and 330), each already of record, for the reasons of record set forth in the previous Office Action dated March 7, 2005 at pages 15-18, as applied to claims 1-3 and 9-13, and further in view of newly cited Applicant's acknowledgement (page 7, line 31-page 8, line 2, page 8, lines 14-15, page 8, lines 22-26 and page 8, lines 31-33), Remington's Pharmaceutical Sciences (16th Edition 1980; p.420-425), Bell et al. (U.S. Patent No. 5,250,534; 1993), Grossman (U.S. Patent No. 6,271,228; 2001), Anderson et al. (U.S. Patent Application Publication 2003/0158223 A1; Filed February 22, 2002) and The Merck Index (Tenth Edition, Monograph No. 8220, "Saralasin").

Present claims 4-8 are properly included in the instant rejection because Applicant has amended the claims to correct improper multiple dependency.

The differences between the Macor et al. reference in view of The Merck Manual of Diagnosis and Therapy (Sixteenth Edition; 1992, p.413-431), Cecil's Textbook of Medicine (Twenty-First Edition, 2000, 273-279 and 1279-1285), and Physician's Desk Reference (55th Edition, 2001; p.323 and 330), each already of record, as set forth in the previous Office Action

at pages 15-18, and the presently claimed subject matter lie in that the combination of references do not teach:

(i) the use of vardenafil; 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-(2-(1-methylpyrrolidin-2-yl)ethyl)-4-propoxybenzenesulphonamide; 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidine-7-one; or 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one or pharmaceutically acceptable salts thereof as PDE5 inhibitors as recited in present claim 4;

(ii) the use of pharmaceutically acceptable salts of sildenafil, especially sildenafil citrate, and combinations of sildenafil citrate and an angiotensin II antagonist as recited in present claims 5, 6 and 8; and

(iii) the use of eprosartan, olmesartan, olmesartan medoxomil, saralasin, telmisartan or pharmaceutically acceptable salts thereof as angiotensin II receptor antagonists.

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(i) Macor et al. broadly discloses the use of a cGMP PDE5 inhibitor in combination with an angiotensin II antagonist for the treatment of cGMP-associated conditions, particularly those that are responsive to the inhibition of cGMP PDE, such as hypertension, angina (stable, unstable and variant type), atherosclerosis, congestive heart failure, and stroke (col.1, lines 55-61 and col.16, line 66-col.17, line 9). Although the use of vardenafil; 3-(1-methyl-7-oxo-3-propyl-6,7-

dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-(2-(1-methylpyrrolidin-2-yl)ethyl)-4-propoxybenzenesulphonamide; 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidine-7-one; or 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one or pharmaceutically acceptable salts thereof as PDE5 inhibitors are not expressly disclosed by the reference, Applicant has acknowledged at page 7, line 31-page 8, line 2, page 8, lines 14-15, page 8, lines 22-26 and page 8, lines 31-33 that such compounds were well known in the art as PDE5 inhibitors. It would, therefore, have been obvious to the skilled artisan at the time of the invention to employ any one of the PDE5 inhibiting compounds named above in the combination therapy (i.e., cGMP PDE5 inhibitor and angiotensin II antagonist) disclosed by Macor et al. Such a person would have been motivated to do so because each one of the PDE5 inhibitors above would have been reasonably expected to function in the same or substantially the same manner to those cGMP PDE5 inhibitors taught by the reference and would have been reasonably expected to effect the same activity and therapeutic effect as those PDE5 inhibitory compounds specifically disclosed by the reference.

Furthermore, the use of pharmaceutically acceptable salts of such compounds would have been a matter well within the purview of the skilled artisan. As taught by Remington's Pharmaceutical Sciences, drugs may be formulated into salts to modify the duration of action of a drug; to modify the transportation and distribution of the drug in the body; to reduce toxicity; and to overcome difficulties encountered in pharmaceutical formulation procedures or in the dosage form itself (see column 2 of page 424, first paragraph). Thus, it would have been obvious to the skilled artisan motivated by any one or more of these factors to formulate the active PDE5

inhibitor into a pharmaceutically acceptable salt to enhance the pharmacokinetic parameters of the drug or to reduce the toxicity with the reasonable expectation that the therapeutic benefit of the agent in salt form it the same or similar to that of the agent itself.

(ii) Although Macor et al. does not expressly disclose the use of sildenafil citrate or other pharmaceutically acceptable salts of sildenafil, but rather discloses the use of sildenafil in general, sildenafil salts, particularly sildenafil citrate, were well known in the art at the time of the invention. Bell et al. (U.S. Patent No. 5,250,534; 1993) discloses the use of pyrazolopyrimidinone compounds useful in the treatment of cardiovascular disorders, including angina, hypertension, heart failure and atherosclerosis. Sildenafil is disclosed at col.20, lines 63-65 of Bell et al. and pharmaceutically acceptable salts thereof are disclosed at col.21, line 7 of Bell et al. Grossman (U.S. Patent No. 6,271,228; 2001) is relied upon to demonstrate that sildenafil citrate was well known in the art at the time of the invention as a cGMP PDE5 inhibitor (col.4, lines 28-41). Thus, it would have been obvious, and well within the purview of, the skilled artisan to employ pharmaceutically acceptable salts, particularly the citrate salt, of sildenafil as a component of the composition disclosed by Macor et al. because such salts would have been reasonably expected to exert the same or similar function as sildenafil itself and would not have been reasonably expected to materially alter the activity of the composition.

Moreover, the use of the sildenafil citrate salt in combination with any one or more of the angiotensin II antagonists taught by Macor et al. or any one or more of the angiotensin II antagonists known in the art at the time of the invention (see below, under "(iii)") would also have been plainly obvious to the skilled artisan in light of the teachings of Macor et al. (i.e., who broadly discloses a PDE5 inhibitor in combination with an angiotensin II antagonist). Thus, the

combinations recited in the presently claimed subject matter of claim 8 would have been well within the purview of the skilled artisan, absent factual evidence to the contrary.

(iii) Macor et al. broadly discloses the use of the angiotensin II antagonist, particularly losartan, irbesartan, valsartan and candesartan, but is silent as to the use of eprosartan, olmesartan, olmesartan medoxomil, saralasin, telmisartan or pharmaceutically acceptable salts thereof. However, such compounds were well known in the art at the time of the invention. Anderson et al. (U.S. Patent Application Publication 2003/0158223; Filed February 22, 2002) teaches the angiotensin II antagonists eprosartan, olmesartan and telmisartan for the treatment of elevated blood pressure and congestive heart failure (page 1, paragraph [0003]) and their pharmaceutically acceptable salts thereof (page 1, paragraph [0031]). The Merck Index teaches the use of saralasin, and its hydrated acetate salt, as an angiotensin II antagonist used as an antihypertensive (see The Merck Index, Tenth Edition, Monograph No. 8820). Thus, it would have been obvious to the skilled artisan to employ any one of the angiotensin II antagonists known in the art in the combination of agents taught by Macor et al. Such a person would have been motivated to do so because any one of these known angiotensin II antagonists would have been reasonably expected to exert the same or similar function to those particularly disclosed by Macor et al. and, thus, would have achieved the same therapeutic benefit.

While it is acknowledged that Anderson et al. teaches olmesartan but is silent as to the use of olmesartan medoxomil as an angiotensin II antagonist, the teaching of olmesartan in general and the teaching of any pharmaceutically acceptable salt of olmesartan is considered to be sufficient teaching to place the use of olmesartan medoxomil (a salt of olmesartan) well within the purview of the skilled artisan.

Response to Applicant's Remarks under 35 U.S.C. 103(a)

Applicant's remarks at pages 15-18 of the amendment have been carefully considered, but fail to persuade the Examiner of error in her determination of obviousness.

Applicant states that the Examiner has failed to establish a *prima facie* cause of obviousness because Macor et al. does not teach the use of a cGMP PDE5 inhibitor in combination with an angiotensin II antagonist for the treatment of hypertension and atherosclerosis and that there is no motivation in the cited references available to one skilled in the art that suggest the combined use of a cGMP PDE5 inhibitor and an angiotensin II antagonist for the treatment of various types of hypertension. Applicant further states that Macor et al. fails to teach or remotely suggest the specific diseases or conditions that can be treated by the combined use of the disclosed compounds and other suitable therapeutic agents and that neither The Merck Manual or Cecil's suggests the combined use of a cGMP PDE5 inhibitor and an angiotensin II antagonist and, thus, one skilled in the art would not be motivated to combine such agents for the treatment of the various types of hypertension. Applicant relies on the data provided at page 20, which Applicant states demonstrates that the efficacy of the combined use of a cGMP PDE5 inhibitor and an angiotensin II antagonist is significantly larger than the sum of the additive effects thereof.

For the reasons stated above in the preceding section entitled "Claim Rejection-35 U.S.C. 102", Macor et al. is considered to expressly teach the use of a cGMP PDE5 inhibitor in combination with an angiotensin II antagonist for the treatment of hypertension, angina (stable, unstable or variant type), congestive heart failure, atherosclerosis or stroke. Although Applicant asserts there is no motivation in the cited references that suggest the combined use of a cGMP

PDE5 inhibitor and an angiotensin II antagonist for the treatment of various types of hypertension, the broad teaching of "hypertension" in general by the Macor et al. reference is considered to be inclusive of hypertension resulting from any one of a variety of etiologies. Thus, despite whether the hypertension results from diabetes or atherosclerosis or is simply essential hypertension, such conditions are still considered "hypertension", and, therefore, are within the scope of the teachings of Macor et al., absent any factual evidence or direction to the contrary.

It is acknowledged that neither The Merck Manual nor Cecil's suggests the combined use of a cGMP PDE5 inhibitor and an angiotensin II antagonist and, thus, one skilled in the art would not be motivated to combine such agents for the treatment of the various types of hypertension. However, neither The Merck Manual nor Cecil's Textbook of Medicine was relied upon to show that the skilled artisan would have been motivated to combine such agents together for the treatment of various types of hypertension. Rather, The Merck Manual and Cecil's were relied upon to show the various types of hypertensive conditions known in the art to fall generally under the category of "hypertension" and also to demonstrate the nexus between hypertension as a condition resulting from diabetes. Thus, Applicant's assertion that The Merck Manual and Cecil's do not suggest the combination of a cGMP PDE5 inhibitor and an angiotensin II antagonist is not relevant to the present rejection because the references were not relied upon to teach such a limitation.

Moreover, Applicant's reliance on the data provided at page 20, which demonstrates that the efficacy of the combined use of a cGMP PDE5 inhibitor and an angiotensin II antagonist is significantly larger than the sum of the additive effects thereof, has been considered, but fails to

provide a basis for concluding that the claimed subject matter would not have been obvious because the results are limited to only a single combination of cGMP PDE5 inhibitor and angiotensin II antagonist, namely the combination of candesartan and the PDE5 inhibitor 3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridine-3-yl]-2-(pyridine-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one. However, the claims subject to this rejection encompass cGMP PDE5 inhibitors and angiotensin II antagonists as groups in general (see claim 1, for example). Further, it has not been argued or demonstrated on the record that the results obtained with candesartan and the PDE5 inhibitor named above would be exemplary of results that would occur with all of the cGMP PDE5 inhibitor and angiotensin II antagonists encompassed by the claims. In this regard, while the single combination of candesartan and 3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridine-3-yl]-2-(pyridine-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one has been tested and has been shown to possess activity beyond what would have been reasonably expected (i.e., greater than additive results), and similarly, just as a single point in space fails to define a line, the results demonstrated for this combination are not deemed sufficient to establish non-obviousness of the presently claimed genus of cGMP PDE5 inhibitors and angiotensin II antagonists.

For these reasons and those set forth in the previous Office Action, claims 1-13 are properly rejected.

### *Conclusion*

Rejection of claims 1-13 is deemed proper and is **maintained**.

No claims of the present application are allowed.

Applicant's amendment correcting the improper multiple dependency of claims 4-8 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-6:00 PM), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Leslie A. Royds
Patent Examiner
Art Unit 1614

August 22, 2005

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